

EDITORIAL



Remdesivir — An Important First Step

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Beigel et al. have provided in the *Journal* the first report of an effective treatment for Covid-19, resulting from a rigorously designed and conducted clinical trial.¹ It is remarkable that a randomized, placebo-controlled trial of a potential antiviral treatment for a disease whose pathogenesis is still not fully defined was carried out at multiple international sites during a pandemic. Conducting such a clinical trial only a few months after SARS-CoV-2 was discovered is an extraordinary achievement.

The reported clinical effect of intravenous remdesivir was relatively modest. The primary outcome was a reduction in time to recovery, from a median of 15 days among placebo recipients to 11 days among those receiving remdesivir. A trend toward lower mortality among patients who received remdesivir (7.1%) than among those who received placebo (11.9%) was also observed, but the difference did not reach statistical significance. The shorter time to recovery led the data and safety monitoring board to recommend unblinding of the data to study team members from the National Institute of Allergy and Infectious Diseases, who subsequently decided to make the results public. The intent was to enable placebo recipients, as well as patients elsewhere, to benefit from treatment with remdesivir. On May 1, 2020, the Food and Drug Administration issued an Emergency Use Authorization for remdesivir to treat adults and children with severe Covid-19.² Remdesivir must be administered intravenously, which represents a limitation to its use.

As is often the case, an initial study raises as many questions as it answers. Analysis of treatment effect according to stratification by clinical status (“baseline ordinal value”) showed an over-

all benefit of treatment with remdesivir. However, the effect on time to recovery was observed largely in patients who entered the study in the severe disease stratum (12 days in remdesivir recipients, as compared with 18 days in placebo recipients). The median time to recovery among those with mild-to-moderate disease was similar in the remdesivir and placebo groups (5 days). Remdesivir did not appear to improve outcomes in patients who required mechanical ventilation or extracorporeal membrane oxygenation, but estimates of time to recovery require further follow-up in this group. The findings in the trial suggest that the timing of initiation of treatment with an antiviral such as remdesivir, as well as the underlying clinical status of the patient, may have important effects on the outcomes of therapy. The trial was also conducted under an adaptive-design platform that allowed participants to receive other therapies for Covid-19 that were permitted by their home institutions. It will be important to identify these cotherapies and any effects they might have on the results.

In an accompanying article by Goldman et al., investigators studied the effects of remdesivir on Covid-19 outcomes when treatment was given for 5 days as compared with 10 days.³ After adjustments for baseline clinical status, the effects of 5 days and 10 days of remdesivir therapy were similar. The absence of a control group in this study did not permit an overall assessment of the efficacy of remdesivir. In our current era of limited remdesivir supplies, priority should be given to a 5-day remdesivir regimen for patients at the early stages of severe disease (i.e., when they are receiving supplemental oxygen but have not yet been intubated), since the evidence for

benefit is clearest in this population. As remdesivir supplies increase and more data accrue, our understanding of the populations that will benefit most from remdesivir therapy may evolve further.

Both trials used ordinal scales to assess patients' clinical status; the scales were similar but not identical. These scales enabled use of the same study protocols at geographically separated sites and permitted rigorous statistical analyses of results. Analysis of the relationship between remdesivir use and clinical status may also have implications for elucidation of the pathogenesis of SARS-CoV-2. Subgroup analyses of study participants in both trials may also help to clarify the effects of factors such as country, race, age, sex, and coexisting conditions on observed outcomes.

Quantitative analyses of virus specimens collected sequentially from different geographic sites and from multiple anatomical locations will be of great interest. Measurement of SARS-CoV-2 viral loads from respiratory-tract specimens collected during the trial conducted by Beigel et al. may provide valuable information on the mechanisms of action of remdesivir and may help to guide appropriate use and timing of treatment with antivirals in the future. It is also apparent that the pathogenesis of Covid-19 involves not only virus replication, but also immunomodulation and inflammation. Sequential studies of biologic markers such as interleukin 6, C-reactive protein, ferritin, and D-dimer should help us better understand the pathogenesis of Covid-19.^{4,5} Studies of combination therapy with other anti-

virals and antiinflammatory agents in appropriate sequence are of high priority, and plans for such studies are already under way.

The report from Beigel et al. shows that remdesivir provides moderate clinical benefit in the treatment of patients with Covid-19. The findings presented are preliminary and are to be followed by a more complete gathering of data and a full statistical study of the entire study population. The initial findings are a step forward on the road to developing effective therapy for SARS-CoV-2 infections and, as such, are an important advance.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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